Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5992 Fax: 609 252-3619

Laurie Smaldone, M.D.
Senior Vice President
Worldwide Regulatory Affairs

November 1, 1999

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 99D-2729; Draft Guidance, *BA and BE Studies for Orally Administered Drug Products – General Considerations, 64 Federal Register 48409 (September 3, 1999)*

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spending totaled $1.4 billion.

For these reasons, we are very interested in and well qualified to comment on this FDA proposal to issue a guidance for industry regarding general considerations for BA and BE studies for orally administered drug products.

Summary of BMS Comments on Proposal

We commend the U.S. FDA for attempting to develop general guidelines for the design, conduct, and analysis of BA and BE studies for orally administered drug products. However, there are several aspects of the proposed guidance that appear contrary to the FDA's stated objectives, which we have cited below.

Specific Comments (Items that Need Clarification & Recommended Actions)

I. Elements Which Should Be Modified

(A) Section II, Part B, Second Paragraph

It is not clear what an inactive moiety is, or under what circumstances it would be

99D-2729

C 5

appropriate to quantify such a species. Further, if such a moiety does not represent a safety concern or contribute to the efficacy of a drug, then the relevance of quantitative analysis is questionable.

Recommendation: We suggest that the reference to 'inactive moieties' be removed from the guidance, or clarify if the reference is to alternative measurable moieties (e.g., when first pass metabolism is high).

(B) Section III, Part A, Number 4.

The guidance specifically addressing the design and analysis of bioequivalence studies is not finalized, and it is therefore premature to make a recommendation requesting replicate study designs in this document. The regulatory burden is also increased by the recommendation that sponsors contact review staff whenever a decision is taken not to conduct a study using a replicate design, as suggested in Section IV.

Recommendation: We recommend that all references to replicate design studies be dropped from this guidance.

(C) Section III, Part A, Number 5.

The draft guidance recommends admitting "as heterogeneous a study population as possible, with a reasonable balance of males and females, young and elderly, and members of differing racial groups". While we agree, in principle, with FDA's desire to include representation of all demographic groups, it is impractical to expect studies to be powered to demonstrate equivalence within each subgroup. The use of the word "balance" has a statistical connotation that implies a factorial study design in which a specific number of subjects in each deomgraphic group are required. This could have the impact of substantially increasing sample size and magnify recruiting problems. Bioequivalence studies, as described in Section IIB, are conducted to evaluate *in vivo* performance of a dosage form as an aspect of documenting product quality. Therefore, in order to focus on the primary objective of determining product quality, it is advantageous to **enroll a relatively homogenous group of subjects**. Admitting a heterogeneous study population may compromise the attainment of this objective. It is also likely that the complexity and resources to conduct the study will increase, as a consequence of having to enroll more subjects to account for additional variability in the subject population, as well as to achieve balance with respect to subgroup demographics. We agree that in some instances it may be advantageous to enroll in a BE study the patient group for which the drug is intended for use; however, even in these situations the inclusion/exclusion criteria will need to be defined to ensure a certain consistency in baseline characteristics.

Recommendation: In order to make this section as clear as possible, the use of the phase "a reasonable balance" should be removed and replaced by the following sentence: Sponsors are encouraged to enroll as heterogeneous a study population as possible.

(D) Section III, Part A, Number 8a and Section V, Part C, Number 2

The draft guidance recommends the use of the early exposure metric for making a regulatory decision about BE; however the need for the use of early exposure is not fully defined. For

example, what constitutes 'appropriate clinical safety and/or efficacy trials and/or PK/PD studies' as justification for use of a partial AUC? What confidence interval limits would have to be met in order to claim equivalence in a partial AUC? Finally, will two products be considered equivalent if CMAX, but not partial AUC, meets the required criteria for concluding bioequivalence (or vice versa: partial AUC, but not CMAX passes)? While there are some instances where early exposure may be an important determinant of efficacy, this information is unnecessary for many drugs and will add an additional regulatory burden.

Recommendation: The use of early exposure as a metric for establishing bioequivalence in all cases is unnecessary and will only impose an additional regulatory burden. The use of early exposure should be suggested only in those instances where it is required for reasons of safety or efficacy (e.g., pain relief).

(E) Section V, Part C, Number 1 and Section V, Part D, Number 2.

Recommendation: Until such time that the guidance on average, population, and individual approaches to establishing bioequivalence is finalized, we recommend that references to individual and population approaches be excluded from this general considerations document.

(F) Section V, Part D, Number 1

Recommendation: It should be clarified that delayed-release drug products are not subject to the requirement to assess steady-state performance.

(G) Section V, Part D, Number 2

It is difficult to rationalize why drugs that exhibit nonlinear kinetics should be uniformly subjected to narrower confidence interval criteria to conclude bioequivalence. Recognizing that a BE study is primarily a quality control tool, the pharmacokinetic characteristics of the drug should primarily influence design elements such as number of subjects studied and sample collection schedule. In some cases, particularly for a chronically administered drug that demonstrates less variability in kinetic parameters at steady state, a multiple-dose study may be more relevant in determining equivalence.

Recommendation: Adjusting the width of the confidence interval should only be done for drugs with a narrow therapeutic index where safety concerns warrant a more conservative determination.

(H) Appendix 2

In some cases, collection of samples for three or more terminal half-lives of the drug does not add meaningful data for the accurate determination of AUC. With the increasing use of ultrasensitive LC/MS methods, it is possible to measure systemic concentrations of a drug for longer intervals; however, the area under the curve represented by these concentrations is a small contribution to the total AUC. Therefore, for drugs with very long apparent terminal elimination phases, it is more meaningful to describe a sampling schedule in terms of the change in concentrations relative to CMAX (for example, samples should be collected until the concentrations fall to 1% of the peak value) or how much of the AUC at infinity is represented (for example, 90%) in the truncated AUC. In addition, there are numerous literature references that support the use of truncated AUCs in the determination of

bioavailability and bioequivalence.[1-4]

We do not see the merit of reporting both the elimination rate constant and elimination half-life. Since half-life is the more widely utilized parameter, we support it being reported (when appropriate) in a BE study. However, we disagree with the recommendation to perform statistical analyses on TMAX and half-life.

Recommendation: Since the focus of a BE study is to ensure the absence of a significant difference in the rate and extent of absorption, the statistical analysis should involve only the parameters that support this objective, i.e., CMAX and AUC.

References

1 Martinez M and Jackson AJ. Suitability of various noninfinity area under the plasma concentration-time curve (AUC) estimates for use in bioequivalence determinations: Relationship to AUC from zero to infinity (AUC(0-INF)). Pharm Res 1991;8:512-517.

2 Bois FY, Tozer TN, Hauck WW, Chen M, Patnaik R and Williams R. Bioequivalence: Performance of several measure of extent of absorption. Pharm Res 1994;11:715-722.

3 Midha KK, Hubbard JW, Rawson M and Gavalas L. The application of partial areas in assessment of rate and extent of absorption in bioequivalence studies on conventional release products: Experimental evidence. Eur J Pharm Sci 1994;2:351-363.

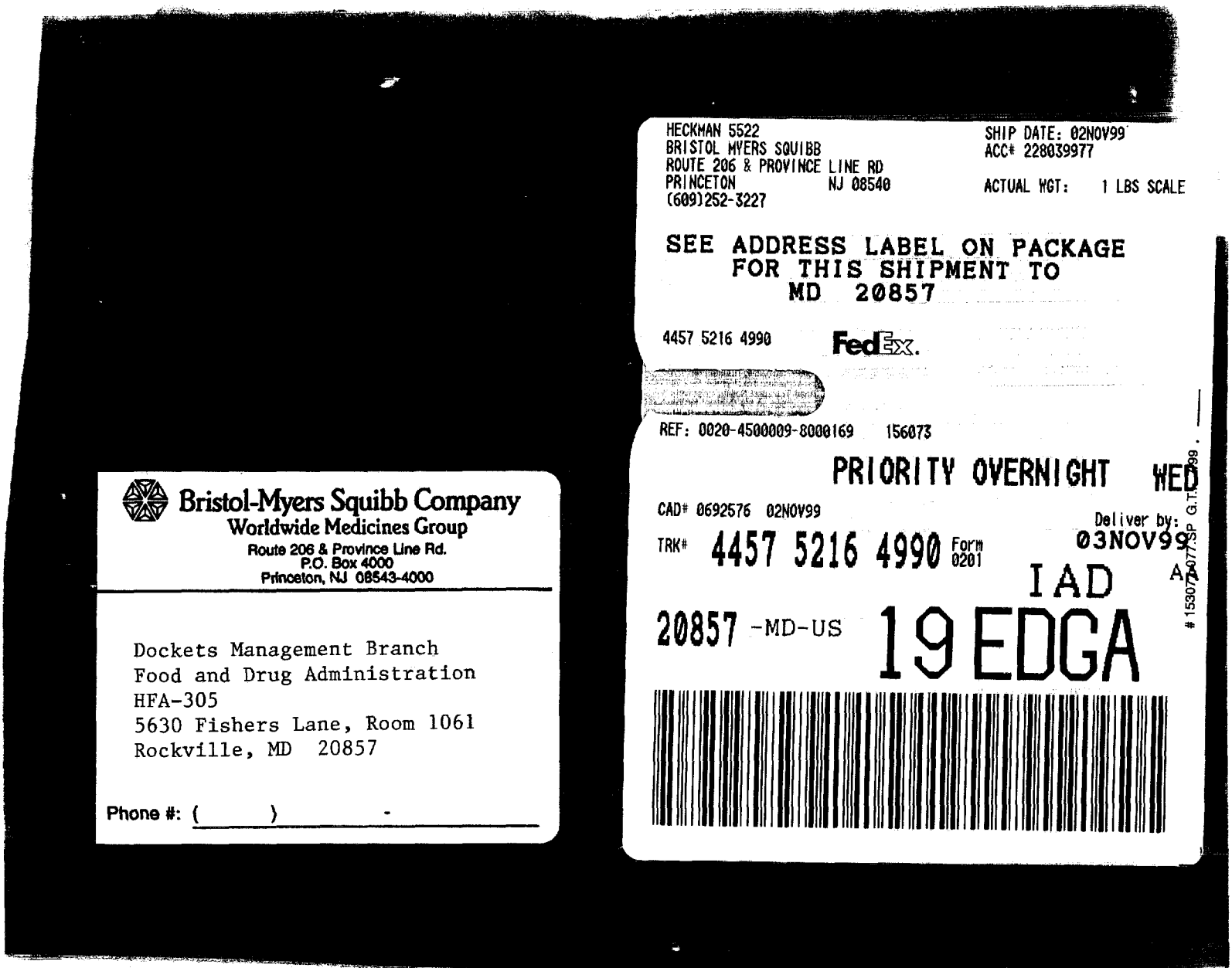
4 Gaudreault J, Potvin D, Lavigne J and Lalonde R. Truncated area under the curve as a measure of relative extent of bioavailability: Evaluation using experimental data and Monte Carlo simulations. Pharm Res 1998;15:1621-1629.

Bristol-Myers Squibb appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

Laurie Smaldone

Laurie F. Smaldone, M.D.
Senior Vice President
Regulatory Science and Outcomes Research



HECKMAN 5522
BRISTOL MYERS SQUIBB
ROUTE 206 & PROVINCE LINE RD
PRINCETON NJ 08540
(609)252-3227

SHIP DATE: 02NOV99
ACC# 228039977

ACTUAL WGT: 1 LBS SCALE

SEE ADDRESS LABEL ON PACKAGE
FOR THIS SHIPMENT TO
MD 20857

4457 5216 4990 FedEx.

REF: 0020-4500009-8000169 156073

PRIORITY OVERNIGHT WED

CAD# 0692576 02NOV99

Deliver by:
03NOV99

TRK# 4457 5216 4990 Form 0201

IAD

20857 -MD-US 19 EDGA

Bristol-Myers Squibb Company
Worldwide Medicines Group
Route 206 & Province Line Rd.
P.O. Box 4000
Princeton, NJ 08543-4000

Dockets Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Phone #: ( ) -